

Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review

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Abstract

Mind-body therapies are commonly recommended to treat vasomotor symptoms, such as hot flushes and night sweats (HFNS). The purpose of this systematic review was to evaluate the available evidence to date for the efficacy of different mind-body therapies to alleviate HFNS in healthy menopausal women and breast cancer survivors. Randomised controlled trials (RCTs) were identified using seven electronic search engines, direct searches of specific journals, and backwards searches through reference lists of related publications. Outcome measures included HFNS frequency and/or severity or self-reported problem rating at post-treatment. The methodological quality of all studies was systematically assessed using predefined criteria. 26 RCTs met the inclusion criteria. Interventions included yoga (n=5), hypnosis (n=3), mindfulness (n=2), relaxation (n=7), paced breathing (n=4), reflexology (n=1) and cognitive behavioural therapy (CBT) (n=4). Findings were consistent for the effectiveness of CBT and relaxation therapies for alleviating troublesome vasomotor symptoms. For the remaining interventions, although some trials indicated beneficial effects (within groups) at post-treatment and/or follow up, between group findings were mixed and overall, methodological differences across studies failed to provide convincing supporting evidence. Collectively, findings suggest that interventions that include breathing and relaxation techniques, as well as CBT, can be beneficial for alleviating vasomotor symptoms. Additional large, methodologically rigorous trials are needed to establish the efficacy of interventions on vasomotor symptoms, examine long-term outcomes and understand how they work.

Introduction

Hot flushes and night sweats (HFNS) or vasomotor symptoms are experienced by 65-80% of healthy menopausal women in Western cultures [1-2]. Women often describe these symptoms as recurrent periods of flushing, sweating and an intense heat sensation on their face and upper chest. HFNS are associated with disturbances of the temperature-regulating mechanism in the hypothalamus, triggered by a natural decline in oestrogen levels during the menopause transition [3]. Symptoms typically begin one year prior to menstrual period cessation and 10–30% of post-menopausal women continue to experience symptoms throughout their lives [4]. Symptoms can disrupt sleep, work and other daily activities [5-6].

HFNS are especially problematic in breast cancer patients, affecting 65-85% of women [7].

Treatments such as chemotherapy or adjuvant endocrine treatments can compromise ovarian function, resulting in rapid reduction of oestrogen levels - the major cause of HFNS [7]. Breast cancer survivors might have more frequent and severe flushes than women who undergo normal menopause [8].

Moreover, HFNS can last for several years, which can reduce treatment adherence [9]. Hormone replacement therapy (HRT), an effective treatment for HFNS, is usually contraindicated, particularly in oestrogen receptors positive cancers, due to cancer reoccurrence risks [10]. Therefore, there is a need among well women and breast cancer survivors for safe and effective non-hormonal treatments that are free from side-effects to support management of HFNS.

Mind–body interventions include methods that are designed to “enhance the mind’s capacity to affect bodily function and symptoms” [11]. Such interventions include relaxation, paced breathing, clinical hypnosis, yoga, mindfulness, reflexology and cognitive behavioural therapies (CBT). Although these interventions have shown promise for the management of menopausal complaints by reducing stress reactivity, enhancing mood, wellbeing and improving sleep [4], their effectiveness for vasomotor symptoms remains less clear. Recent meta-analyses have emphasised the need for large randomised clinical trials (RCTs) to generate a sufficient evidence base to guide future clinical treatment decisions around the use of mind-body therapies for troublesome vasomotor symptoms [5, 12]. In addition, three recent commentaries or position statements have been published; however recommendations vary

including the use of CBT and clinical hypnosis [13] to hormone replacement therapy [14], selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) [15]. None of these statements were based on systematic review of the available literature of mind-body interventions for vasomotor symptoms. A recent systematic review of non-hormonal treatments of vasomotor symptoms did not include mind-body therapies [16]. Although a systematic review was published previously on this topic [17], it was based on searches which are now seven years old and did not include the more recent RCTs that have utilised CBT based interventions. The inclusion of CBT based interventions is important as behavioural and cognitive components of CBT may provide women with helpful behavioural strategies and awareness of activities that might trigger HFNS. In addition, the skills developed as part of CBT based programmes can give women a greater sense of control over their HFNS leading to symptom reduction. A UK NICE guidance [14] report focused only on papers that used frequency of HFNS as an outcome which lead to the exclusion of some mind-body trials; we include frequency, severity and problem-rating as HFNS outcomes in this review. The aim of this systematic review was to critically evaluate evidence from available RCTs regarding the efficacy of mind-body therapies to alleviate HFNS in healthy, menopausal women and breast cancer survivors. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] were used. We also outline major limitations in the current literature and discuss directions for future research.

Methods

Inclusion criteria

RCTs published in peer-reviewed journals examining the effects of mind-body interventions (yoga, relaxation, paced breathing, mindfulness, clinical hypnosis, reiki, pilates, reflexology, CBT) on HFNS for women who were either a) peri or post-menopausal or b) breast cancer survivors or in active treatment for breast cancer and c) were experiencing troublesome HFNS. Outcome measures included

HFNS a) frequency and/or b) severity or problem rating at post-treatment. Only trials reported in English were included.

Exclusion criteria

We excluded trials in which pharmaceutical treatments were studied as the main treatment unless they constituted a comparison condition or trials which did not specifically target HFNS symptoms. Case series and case studies were also excluded as were trials published in dissertation or abstract form or that did not report quantitative outcome data.

Search strategy

The databases Pubmed, Medline, PsycInfo, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Web of Science and Embase were searched from January 1980 and up to 31st December 2015. Key term searching was undertaken (Table 1). Retrieval was limited to RCTs, English language and human participants (see Figure 1). Organic backwards (reference list search) and forward (citation search) searches were undertaken to identify additional relevant papers. No meta-analysis was performed due to the heterogeneity of the studies, e.g. variation in the menopausal status of women or length of treatments. However, where possible, and to allow comparisons across studies, we calculated effect sizes (Cohen's *d*) [19] in measures of HFNS (frequency, severity or problem rating) for each study, separately (Tables 2 and 3).

Quality ratings

Study quality was evaluated using a standard quality assessment tool [20] using 14 established criteria (e.g. related to study rationale, study design, sample sizes). Quality ratings were conducted independently by two authors and minor differences were settled before deciding on the final scores (maximum possible score of 1). Quality ratings for included studies are also shown in Tables 2 and 3.

Risk of bias

Risk of bias was evaluated using the Cochrane Collaboration's tool for assessing risk of bias (adapted from Higgins and Altman [21]) which covers: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting).

Results

Yoga

Yoga is an Eastern spiritual discipline which includes breath control, simple meditation, and the adoption of specific bodily postures and can often be practised for promotion of health and relaxation. Many different styles of yoga exist, which vary in intensity, physical effort and relaxation component [22].

1487 studies were identified. 1478 papers were excluded for not meeting inclusion criteria. 9 full-text articles were assessed. Two studies were not available in English [23-24] and two studies used the same participant population [25-28]. Therefore, 4 RCTs for healthy women [26, 28-30] and 1 for breast cancer survivors [31] were included.

There was heterogeneity amongst studies employing various forms of yoga interventions with some being essentially meditative [31], whereas others focusing on breathing [26, 30, 31] or addressing physical positions [28-30]. Interventions lasted for 2-4 months; only one RCT [31] reported a long-term follow-up.

Overall, findings appear to be inconsistent regarding their effectiveness in alleviating symptoms, with some RCTs showing no HFNS efficacy compared to either exercise or control conditions [26-27, 30] or beneficial efficacy for HF but not NS compared to control conditions [31]. One RCT showed significant reductions in HFNS when compared to control but not exercise groups [29]. Additionally, in breast cancer survivors [31] although the yoga group improved with regard to symptom reporting, the reduction score was only 31%, which is similar to the placebo response seen in other trials [32].

Reflexology

Reflexology includes massage of certain areas of the feet and hands that correspond to certain glands, organs, and other parts of the body; local finger pressure may influence the function of organs and promote homeostasis, relaxation, allowing a healing process [33].

102 studies were identified. 97 papers were excluded. Five full text articles were assessed. Four studies were further excluded as not available in English [34-36] or not examining HFNS as an outcome measure [37]. One RCT [33] for healthy women was included and comparison of 9 weeks of standard foot reflexology and routine foot massage reported no significant between-group differences in HFNS.

Relaxation

As central noradrenergic activity can be increased in women experiencing HFNS, relaxation may reduce sympathetic activity, and consequently, HFNS reporting [38-39].

83 studies were identified. 71 papers were excluded and 12 full-text articles were assessed. Two studies used the same breast cancer population [35-36] in more than one article. 7 RCTs for healthy women and 4 for breast cancer survivors were therefore included.

Applied relaxation therapy

Applied relaxation therapy includes a number of systemic approaches to relaxation including PMR (e.g. repeatedly tensing and then releasing muscle groups), release-only relaxation (releasing muscle groups directly), cue-controlled relaxation (linking release-only relaxation to breathing), differential relaxation (practising skills in a range of situations), rapid relaxation, application training and maintenance program [51]. 7 RCTs were included. Interventions lasted for 6-12 weeks and follow-up periods ranged from 3 to 6 months. An early trial of PMR [44] for heat stress induced symptoms in a laboratory setting showed beneficial effects in HFNS frequency in the menopausal but not control group. Irvin et al [50] yielded significant reductions in HFNS intensity (but not frequency) in the relaxation group at post-treatment. Nedstrand et al [42], applied relaxation (compared with estradiol

treatment (ET)) and HFNS frequency decreased significantly in both groups and remained significant at 6 months follow-up. Nevertheless, reductions were faster in the ET group than in the relaxation group. Zaborowska et al [43] reported a significant reduction in HFNS frequency in the relaxation group compared to the placebo (but not the other comparators: acupuncture or ET) group.

In a pilot study[48] no between group differences in HFNS was observed between relaxation training using deep breathing and guided imagery when compared with a waitlist condition. Nedstrand et al [40] compared relaxation with acupuncture and again, although both groups improved in HFNS frequency, there were no significant between-group differences at post-treatment or follow-up. More recently, Fenlon et al [49] compared applied relaxation (deep breathing, muscle relaxation and guided imagery) with a waitlist control group. There was a significant reduction in both flush frequency and severity ratings at post-treatment compared to the control group; severity, but not frequency, improvements were sustained at follow-up.

Paced respiration

Paced respiration involves taking 6 to 8 slow deep breaths per minute while inhaling through the nose and exhaling through the mouth [47]. Four RCTs were included. Interventions lasted for 4-16 weeks and only one RCT reported a follow-up period [47].

Freedman and Woodward [45] reported decreased HFNS frequency following paced-respiration compared with progressive muscle relaxation and electroencephalographic biofeedback (control groups) using physiological measurement of HFNS frequency. Subsequently Freedman and colleagues [46] compared paced respiration with EEG biofeedback again and showed similar results for paced respiration. Nevertheless, in Huang et al [52], a paced respiration intervention using a portable guided-breathing device was significantly less effective than a music-listening intervention in decreasing both frequency and severity of HFNS.

Carpenter et al [47] compared paced respiration, an attention control condition of fast shallow breathing, or usual-care control but no significant changes were found between groups.

Mindfulness / Mindfulness-Based Stress Reduction (MBSR)

Mindfulness encourages individuals to discriminate more accurately between thoughts, feelings and physical sensations whilst developing a non-reactive awareness of these [53]. 53 studies were identified. 46 papers were excluded for not meeting inclusion criteria. 5 papers were further excluded for not being an RCT [54-55] or did not use HFNS as an outcome measure [56-58]. Therefore, two RCTs were included in the final analysis. Carmody et al [59] reported beneficial effects of MBSR on HFNS bother (but not HFNS frequency) at 9 and 20 weeks post-treatment. Bower et al [61] compared a mindfulness intervention group or to a wait-list group. The intervention led to significant reductions in HFNS although effects were not maintained at 3-months follow-up.

Hypnosis / Mental Imagery

Hypnosis aims to create a deeply relaxed state using mental imagery where individuals are guided to respond to the therapist's suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought, or behaviour[62]. It is argued that regular practice of clinical hypnosis improves parasympathetic tone, resulting in reduced HFNS symptoms [63].

78 studies were identified. 75 papers were excluded. Three full-text articles were assessed. Two RCTs examined the possible effects of hypnosis on HFNS in breast cancer survivors [64-65] and one RCT [63] in well women. Interventions lasted for 5-8 weeks and only one RCT reported a follow-up period [63].

Elkins et al [64] showed that breast cancer survivors who received five weekly sessions of clinical hypnosis experienced fewer HFNS compared to a waitlist control group; also, a 69% reduction in hot flushes relative to baseline. In another trial [65], breast cancer survivors who received eight weekly sessions of hypnosis experienced a 80% reduction in hot flushes at post-treatment relative to baseline, although it should be noted that the sample size was small (N=15).

One RCT [63] was identified in healthy women showing that hypnosis resulted in significant reductions in both self-reported and physiologically measured HFNS compared to a structured control condition; findings remained significant at 12 week follow-up.

Cognitive Behavioural Therapy (CBT)

The CBT approach aims to help individuals to moderate change overly negative cognitions (thoughts and beliefs) and unhelpful behaviours in order to help alleviate troublesome emotional and/or physical symptoms and improve their quality of life.

26 studies were identified. 22 papers were excluded for not meeting the inclusion criteria.

Consequently, four RCTs were included in the final analysis. Two RCTs were carried out in breast cancer survivors [71-72] and two in healthy women [73-74]. In Mann et al [71], group CBT significantly reduced HFNS problem rating at 9 weeks post-treatment compared with usual care and improvements were maintained at 26 weeks follow-up (MENOS 1). Duijts et al [72], women randomly assigned women to CBT, physical activity (PE), CBT and PE combined or control group. The groups that included CBT showed a significant decrease in HFNS problem rating at 12-week post-treatment and 6-month follow-up.

Ayers et al [73] showed significant reductions in HFNS problem rating and NS frequency in Group and Self-Help CBT at post-treatment and follow-up compared to the usual care group (MENOS 2). Furthermore, Keefer et al [70], compared 8 weekly sessions of Group CBT to a waitlist control condition, and found that CBT significantly reduced HFNS frequency compared to the waitlist control at the end of treatment. Nevertheless, the sample size was quite small.

Reiki/Pilates

We did not find any RCTs examining the effects of reiki or pilates on HFNS.

Discussion

The aim of this systematic review was to examine available evidence to date regarding the efficacy of a range of mind-body therapies to alleviate HFNS in well women and breast cancer survivors. The majority of the interventions focused on hot flush frequency as the main outcome. Fewer studies focused on ratings of hot flush severity or problem ratings. Of those that did, reductions in hot flush problem or severity ratings were reported for interventions utilising applied relaxation training (breast

cancer patients), paced respiration (healthy women), mindfulness (healthy women) and CBT (healthy women and breast cancer patients).

CBT, including paced respiration was shown to be effective for HFNS for breast cancer survivors [70] and healthy, menopausal women [73]. Moreover, during interviews conducted at the end of these trials [71, 73] women reported positive experiences of the intervention and considered paced breathing as particularly helpful [83-84]. Findings from this review suggest that interventions that include breathing and relaxation techniques may help reduce HFNS reporting in well women, although evidence was less strong for paced breathing applied to breast cancer survivors [47]. Nevertheless, since RCTs often combined paced breathing or other relaxation exercises with other therapies, such as mental focusing [50] or CBT [71, 73], future studies need to delineate their efficacy as stand-alone treatments.

Overall, we found no consistent beneficial efficacy of yoga for HFNS compared with control groups, although improvements in other troublesome physical symptoms have been reported (e.g. fatigue [75], nausea and vomiting [76]). Neutral or positive effects of yoga have also been reported on quality of life and well-being for both well women [77] and breast cancer survivors [78-79]. For instance, a recent Cochrane review reported no differences between yoga and exercise in vasomotor symptom relief [80], making it thus difficult to differentiate the effects of yoga from engaging in other physical activities. In fact, exercise has not been found to impact upon HFNS over and above control conditions in recent trials [81-82]. Although yoga may have other benefits, its efficacy for alleviating HFNS is, therefore, yet to be established [12].

Finally, there were few RCTs examining the effects of reflexology, clinical hypnosis or mindfulness-based interventions for troublesome HFNS; although some trials of self-hypnosis and mindfulness reported promising results for both breast cancer survivors and well women, there is still insufficient research to consider any as evidence-based treatments.

Possible mechanisms behind the beneficial effects of mind-body interventions on HFNS

While underlying mechanisms remain unclear, there are several ways in which mind-body interventions might alleviate troublesome vasomotor symptoms. Behavioural interventions, such as

hypnosis, mindfulness and/or other relaxation therapies are reported to reduce sympathetic activity, decrease sympathoadrenal reactivity, and enhance parasympathetic output, which may, in turn, reduce HFNS reporting [4, 85]. Such interventions may also reduce symptoms by improving other indices of psychological and physical health. For instance, interventions involving physical activity, such as yoga, have been reported to reduce body fat and improve lipid profiles [86], as well as alleviate stress and low mood difficulties [87], which have, in turn, been associated with HFNS problem rating and severity [88]. Moreover, changes in other lifestyle factors (e.g. diet, smoking) might also be associated with the beneficial effects of behavioural interventions on symptom reporting [89]. Mindfulness-based interventions might enable individuals to be less reactive to stressors and foster adaptation to troublesome symptoms in an effective way [90-91]. Although more large RCTs are needed to establish their efficacy on HFNS, such interventions might be promising for managing stressors that can accompany the menopausal transition.

In regards to possible mechanisms of action of CBT in reducing vasomotor symptoms, the cognitive component of CBT encourages women to identify and challenge negative thoughts and/or beliefs about themselves and their symptoms [92]. The behavioural component of CBT involves increasing women's participation in pleasurable activities, such as relaxation and exercise. CBT may thus provide helpful behavioural strategies and awareness of activities that might trigger HFNS [94]. Such skills can provide a greater sense of control over HFNS, which has been associated with symptom reduction [71, 73, 94-95]. By reducing emotional distress associated with the occurrence of flushes, CBT may also ameliorate reactions to HFNS that would otherwise exacerbate them [93]. Hunter and Chilcot reported that negative beliefs about HFNS were the strongest predictors of problem rating [97] and treatment effects on HFNS problem rating scores have been shown to be mediated by changes in beliefs about coping/control of HFNS and sleep [98]. CBT might work mainly at the level of symptom perception and cognitive appraisal where attention training away from bodily experiences and balancing overly negative appraisals might help to improve women's experiences of HFNS [99].

Methodological quality of studies

Not all participants completed the interventions in the examined studies and data were not always analysed on an intention-to-treat basis. This may have introduced bias, overestimating the benefits of examined interventions. Only some of the studies reported treatment adherence rates, of which some studies indicated that adherence was positively associated with better outcomes. Whether adherence to the treatment sessions was affected by cancer-related symptoms or side-effects of cancer treatment was not reported; similarly, not all studies reported adverse effects and reasons for dropouts. Finally, since the control groups usually consisted of usual care, researchers and participants were not blinded to the interventions, possibly introducing bias. Future studies should ensure rigorous methodology and reporting, mainly adequate randomization, allocation concealment, intention-to-treat analysis, and blinding of at least outcome assessors. Future studies would also benefit from examining outcomes in terms of both the frequency of symptoms and the severity of self-reported problems associated with the symptoms. In addition, clear descriptions of the interventions should be provided together with a description of expertise of the instructors. Finally, although there was heterogeneity of the included interventions it is likely that different interventions share common techniques or common mechanisms. Therefore, to support understanding of why interventions may, or may not, work it is necessary to examine the efficacy not only of the global intervention but also of the components within interventions that may influence intervention efficacy. This would help support the optimal design of future interventions.

Limitations

We excluded other cancer populations where HFNS can be particularly problematic [100]. We also excluded exercise as a mind-body intervention but reviews were recently conducted in this area [80, 82]. Few RCTs included long-term follow-ups, thus findings remain unclear in terms of the longer effects of the examined interventions for vasomotor symptoms. Findings from healthy women may not generalize to women with breast cancer or other populations because of differences in the underlying aetiology of HFNS [99, 102]. In addition, although HFNS in the groups appear to be physiologically similar [103], the higher frequency and severity of symptoms experienced in breast cancer survivors may require more intensive therapies [104]. Additional testing in more diverse

groups is thus warranted. Placebo effects have been observed in trials evaluating complementary therapies for vasomotor symptoms [105]. However, some studies indicated sustained benefits post-intervention, when the placebo effects would be expected to diminish. Finally, not all trials included comparison conditions that controlled for non-specific effects of treatment; such effects cannot therefore be ruled out.

Conclusion

This systematic review found little to moderate evidence for long term effectiveness of clinical hypnosis, yoga, mindfulness and reflexology interventions for vasomotor symptom relief in healthy menopausal women and breast cancer patients. Consequently, there is still insufficient research to consider any as evidence-based treatments. Findings were more consistent for the effectiveness of CBT and relaxation therapies. In line with the recommendations of the North American Menopause Society [13] this review supports the use of CBT as a relatively risk free non-pharmaceutical therapy for the management of vasomotor symptoms. Although NAMS recommend the use of clinical hypnosis, this analysis suggests that further trials are required. Mind-body interventions may offer a safe and inexpensive alternative to HRT treatments, particularly for women seeking non-hormonal therapies either instead of HRT or in addition to it. More rigorous research is needed to compare the effectiveness of mind-body interventions and to understand how these interventions work.

Declaration of Interest statement

The authors report no conflicts of interest.

Current knowledge on the subject

- Mind-body interventions have shown promise for the management of menopausal complaints including enhanced mood, wellbeing and improved sleep
- Recent position statements regarding the management of menopausal symptoms make different recommendations regarding the role of mind-body interventions

What this study adds

- We critically evaluate evidence from available randomised controlled trials regarding the efficacy of mind-body therapies to alleviate vasomotor symptoms in healthy, menopausal women and in breast cancer survivors
- We found little to moderate evidence for long term effectiveness of clinical hypnosis, yoga, mindfulness and reflexology interventions for vasomotor symptom relief in healthy menopausal women and breast cancer patients.
- In line with the recommendations of the North American Menopause Society this review supports the use of CBT as a relatively risk free non-pharmaceutical therapy for the management of vasomotor symptoms

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Figure 1: Flow chart of identification and selection of studies

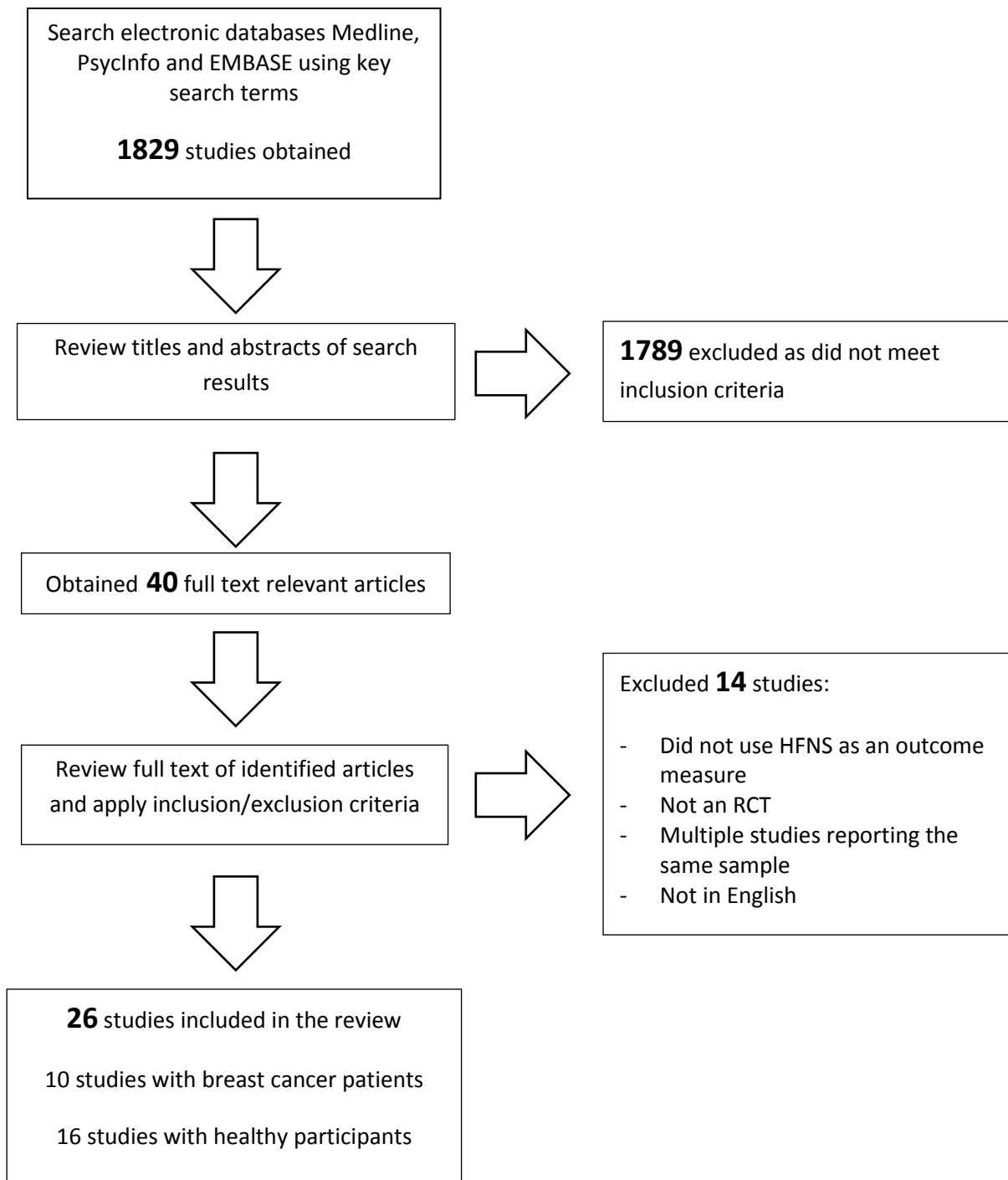


Table 1: search terms

mind-body terminology

relaxation OR applied relaxation OR progressive muscle OR PMR OR yog\$ OR breathing OR paced breathing OR paced-breathing OR mind body OR mind-body OR pilates OR reiki OR reflexology OR meditation OR mindfulness OR hypnosis OR imagery OR complementary therap\$ OR alternative therap\$ OR cognitive behavioural therapy OR CBT]

AND menopaus\$ OR peri-menopaus\$ OR post-menopaus\$ OR climacter\$ OR well women OR well-women OR vasomotor OR hot flash\$ OR hot-flash\$ OR hot flush\$ OR hot-flush\$ OR night sweat\$ OR night-sweat\$].

The above procedure was repeated for breast cancer women alone with “breast cancer OR cancer OR cancer survivors” replacing menopaus\$ OR peri-menopaus\$ OR post-menopaus\$ OR climacter\$ OR climacter\$ OR well women OR well-women”.

Table 2. RCTs recruiting healthy menopausal participants

Author (s), year	Country	Study Population	Intervention	Comparison Condition(s)	Measures	Findings	Cohen's <i>d</i>	Quality ratings
YOGA								
Elavsky & McAuley, 2007 ¹	USA	164 pre, peri, and post-menopausal women 42–58 yrs Race: White (83%) (no HRT)	4 months Iyengar Hatha (breathing and posture practices, meditation): 90 min*2/wk classes and home practice	4 months (1) Walking: 1 hr*3/wk classes and home-individualized exercise 1-2 days/wk (2) Waitlist control	GCS (HFNS bother)	Yoga vs. control: <i>ns</i> Yoga vs. walking: <i>ns</i> Adherence (<i>ns</i>): Walking (70%) > yoga (63%)	<i>d</i> =0.2 <i>d</i> =0.1	0.7
Chattha et al, 2008 ²	India	120 peri-menopausal women 40–55 yrs (no HRT)	2 months IAYT (breathing and posture practices, meditation) Classes: 1Hr*5 /wk	2 months (1) Stretching exercise classes 1Hr*5 /wk	VCL (HFNS severity)	HFNS severity: <i>ns</i> Adherence: 90%	HF: <i>d</i> =0.2 NS: <i>d</i> =0.3	0.8
Afonso et al, 2012 ³	Brazil	61 post-menopausal women 50–65 yrs (no HRT)	4 months Yoga (asana, bhastrika, relaxation) classes: 60 min*2/wk	4 months (1) Passive stretching 60 min*2/wk (2) Waitlist control	KMI (HFNS severity)	Yoga vs. stretching: <i>ns</i> Yoga<waitlist Adherence: 74%	<i>d</i> =0.2 <i>d</i> =0.9	0.6
Newton et al, 2014	USA	249 peri- or post-menopausal women or with hysterectomy	3 months Yoga (breathing exercises, physical	3 months (1) exercise (2) usual activity	Diary (HFNS frequency,	Yoga vs. exercise: <i>ns</i> Yoga vs. usual activity: <i>ns</i>	Unable to calculate	0.8

		40-62 yrs	postures and meditative practice) classes: 90 min * 1/wk and home practice		bother)	Adherence: 95%		
MINDFULNESS								
Carmody 2011 ¹⁴	USA	110 peri or postmenopausal women ≥ 5 HFNS/day (moderate to severe) 47–69 yrs (incl. cancer survivors ≥ 6 months from treatment completion)	9- weeks and 3 month follow-up 8 MBSR (2.5h) classes (n=25) plus one day class on the 6 th week. (body scan, sitting meditation attending to thoughts and emotions, bodily sensations and breathing; stretching exercises) Two CDs for home practice (45 min* 6 days/week)	Waitlist control	Diary [HFNS bother, intensity (frequency x severity)]	HFNS bother: MBSR < C HFNS intensity: <i>ns</i> Adherence: 81%	Unable to calculate	0.8
RELAXATION								
Germaine, 1984 ¹⁵	USA	14 postmenopausal women ≥ 2 HFNS/day 44–61 yrs 12 premenopausal women/controls	6 weeks and 6 month follow-up (Heat stress induction) PMR training: (16, 7 and 2 muscle groups for 2 sessions each)	6 weeks and 6 month follow-up (Heat stress induction) α -EEG biofeedback (control): 1 hr*1/wk and home practice:	Diary (HF frequency)	PMR < C at post-t and FU	Unable to calculate	0.5

		22-45 yrs	1 hr*1/wk and home practice: 2x/day	2x/day				
Irvin, 1996 ¹⁶	USA	33 postmenopausal women ≥ 5 HFNS/day 44-66 yrs	10 weeks RR training: (mental focusing using diaphragmatic breathing and breath awareness) 3 (60 min) sessions* 10 wks, then audio tape for home practice ≥ 20 min*1/day	10 weeks Reading (Placebo) Training: 3 (60 min) sessions* 10 wks, then audio tape for home practice ≥ 20 min*1/day Charting (control)	Diary (HFNS frequency, intensity)	Frequency: <i>ns</i> Intensity: RR < C groups Adherence: 74%	Unable to calculate	0.7
Nedstrand, 2005 ¹⁷	Sweden	30 postmenopausal women with moderate to severe symptoms 48-63 yrs	12 weeks and 6 month follow up AR groups (n=4-6): 60 min*1/wk plus home practice \geq 1/day	12 weeks and 6 month follow up ET (17 β estradiol) 2 mg* day	Diary (HFNS frequency)	HFNS frequency decreased in both groups but faster in ET ET < AR at post-t and FU Adherence: 94%	Unable to calculate	0.8
Zaborowska et al, 2007 ¹⁸	Sweden	102 postmenopausal women	12 weeks AR groups (n=4-6) 60 min* 1/wk plus home practice ≥ 1 /day	12 weeks AT (fixed points, 5-20 mm) plus electrical stimulation (4 fixed points, 2 Hz) 30 min* 2/wk for the first 2 weeks and then 30 min*	Logbook (HFNS frequency)	ET < AR, placebo AR vs. AT: <i>ns</i> AR, AT < placebo	Unable to compute	0.8

				1/wk for another 10 weeks ET (17b-estradiol) 2 mg/day*12 wk Placebo tablets				
PACED RESPIRATION (PR)								
Freedman, 1992 ¹⁹	USA	33 postmenopausal women ≥ 5 HFNS/day White (64%)	4 weeks Paced Respiration training: 1 hr*2/wk	4 weeks Muscle relaxation (MR) training: 1 hr*2/wk α -wave biofeedback (Placebo Control) Training: 1 hr*2/wk	SSC monitoring (HFNS frequency)	PR < MR, C	Unable to calculate	0.5
Freedman et al, 1995 ²⁰	USA	24 postmenopausal women ≥ 5 HFNS/day White (66.67%)	16 weeks 8 PR training sessions: 1 hr*biweekly	16 weeks α -wave biofeedback (Placebo Control) Training: 1 hr*2/wk	SSC monitoring (HFNS frequency)	PR < C	Unable to calculate	0.5
Huang et al, 2015	USA	123 peri- or post-menopausal women ≥ 4 HFNS/day*w/k White (60%)	12 weeks 15 min in-person instruction and home practice 15 min*day	12 weeks Music-listening device without guiding breathing	Diary (HFNS frequency, severity)	PR > C		0.9

REFLEXOLOGY								
Williamson et al, 2002 ²¹	UK	80 symptomatic women \geq 3 months 45-60 yrs (no HRT)	19 weeks and 1 month follow-up 9 sessions using precision reflexology (45 min)	19 weeks and 1 month follow-up 9 sessions of foot massage without any reflexology strokes (45 min)	HFNS frequency HFNS severity	Frequency, severity: <i>ns</i> Adherence: 96%	HFNS frequency: Unable to compute HF severity: <i>d</i> = 0.1 NS severity: <i>d</i> =0.2	0.6
HYPNOSIS								
Elkins et al, 2013 ²²	USA	187 postmenopausal women \geq 7 HFNS/day or \geq 50 HFNS/wk	6 weeks and 3 months follow-up Individualized sessions (45 min) (mental imagery for coolness, safe place imagery, relaxation) plus self-hypnosis CD used for daily home practice	Structured attention control condition	HFSD [HFNS frequency, score (severity x frequency)] SSC monitoring (HFNS frequency)	HFNS frequency: H< C HFNS score: H< C at post-t and FU Adherence: 94%	HFSD frequency: <i>d</i> = 1.27 score: <i>d</i> = 1.21	0.8
CBT								
Keefer and Blanchard, 2005 ²³	USA	19 peri or postmenopausal women	8 weeks Group CBT 90 min sessions (psychoeducation, paced respiration, cognitive restructuring) plus paced respiration home practice	Waitlist	Diary (HFNS frequency, problem rating)	Frequency: CBT < WL	Frequency: <i>d</i> =0.8 Problem rating: <i>d</i> =0.4	0.7
Ayers et al,	UK	140 women \geq 10	6 weeks and 26		HFRS	Problem rating, NS		0.9

2012 ²⁴		problematic HFNS/week for ≥ 1 month	weeks follow-up Group CBT Self-Help CBT	Usual care	(HFNS frequency, problem rating) SSC monitoring (HFNS frequency)	frequency: CBT < UC at post-t and FU		
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Key: IAYT=Integrated Approach to Yoga Therapy; GCS=Greene's Climacteric Scale; KMI = Kupperman Menopausal Index; AT= Acupuncture Therapy; SNI=Superficial needle insertion; ET= estrogen therapy; SA= Sham Acupuncture; WSCL=Wiklund Symptom Check List; Pittsburgh Sleep Quality Index; HFRDIS =Hot Flash Related Daily Interference Scale; MENQOL=Menopause-Specific Quality of Life; ISI=Insomnia Severity Index; Menopausal Symptom Questionnaire; MBSR=mindfulness-based stress reduction; SCL-90-R=Hopkins Symptom Checklist; PSS=Perceived Stress Scale; WHIIRS=Women's Health Initiative Insomnia Rating Scale; KI=Kupperman Index; EPI=Eysenck's Personality Inventory; PSQI =Pittsburgh Sleep Quality Index; UQOL =Utian Quality of Life Scale; SWLS= Satisfaction with Life Scale; PMR=Progressive Muscle Relaxation; MIS= Menopausal Index Scale; POMS =Profile \$Mood Scale; MRS=menopausal rating scale

Table 3. RCTs recruiting women with a diagnosis of breast cancer

Author(s), year	Country	Study Population	Intervention	Comparison Condition	Measures	Findings	Effect sizes	Quality ratings
YOGA								
Carson et al., 2009 ¹	USA	37 early cancer survivors with ≥ 1 HFNS/day* ≥ 4 days/wk 54.4 \pm 7.5yrs Race: White (81.1%) (no HRT)	2 months and 3 month follow-up Yoga Awareness Classes[gentle postures, meditation, and breathing exercises]: 120min*1/wk and daily home CD practice	2 months and 3 month follow-up Waitlist control	HF frequency, severity HF total (frequency x severity) NS frequency	HF frequency, severity, total: Yoga < Waitlist at post-t and FU Adherence: 81%	Unable to calculate	0.7
MINDFULESS								
Bower et al, 2015	USA	61 women with early stage breast cancer at or before age 50	6 weeks and 3 month follow up Mindful Awareness Practices (MAPS) intervention group	6 weeks and 3 month follow up Wait-list control group	HFNS frequency	MAPS < Waitlist at post-t only	Unable to calculate	0.9
HYPNOSIS								
Elkins et al, 2008 ⁷	USA	60 cancer survivors ≥ 14 HFNS/wk for ≥ 1 month	5 weeks 50 min sessions (mental imagery; suggestions for relaxation and coolness; dissociation from HFNS; positive	Waitlist	HFNS total score (severity x frequency)	HFNS total score: H < C	Unable to calculate	0.6

			suggestions; imagery for the future) plus home practice (CD)					
David et al, 2013 ⁸		15 women with breast cancer or an increased risk of breast cancer ≥ 1HFNS/day 42-63 yrs	8 weeks 60 min sessions plus home practice (CD)	Gabapentin 900 mg/day in three doses (control)	Diary (HFNS severity, frequency)	<i>ns</i>	Unable to calculate	0.6
RELAXATION								
Fenlon, 1999 ⁹	UK	24 (non-metastatic) patients with troublesome HFNS 29–74 yrs White (100%)	Relaxation (deep breathing with guided imagery): 2 weekly sessions and home practice	Waitlist	VAS (HFNS frequency, problem rating)	<i>ns</i> Adherence: 71%	Unable to calculate	0.7
Nedstrand et al, 2006 ¹⁰	Sweden	38 postmenopausal women ≥ 2HFNS/day 30–64 yrs (no HRT ≤ 3 months)	12 weeks and 6 month follow up AR groups (n=5-6) 60 min*1/wk and home practice: ≥ 15-20/day	12 weeks and 6 month follow up AT (8 fixed points, 5-20 mm) plus electrical stimulation (4 fixed points, 2 Hz) 30 min*2/wk for 2 wks, then 30	Diary (HFNS frequency)	<i>ns</i> Adherence: 82%	<i>d</i> = 0.1	0.7

				min*1/wk for 10 wks				
Fenlon, 2008 ¹¹	UK	150 postmenopausal women 36–77 yrs White (93%) (no HRT)	4 weeks and 3 month follow-up Relaxation (deep breathing with guided imagery and muscle relaxation): One 60-min, 1:1 session, then audio tape 20 min*day for 4 weeks (home practice)	60 min with a specialist nurse discussing HFNS (control)	Diary (HFNS frequency, severity)	Frequency: R<C at post-t Severity: R<C at post-t and FU Adherence: 60%	Unable to calculate	0.8
PACED RESPIRATION								
Carpenter et al, 2012 ¹²	USA	218 women (96 cancer survivors; 122 healthy women) cancer survivors (non-metastatic) > 4 weeks after treatment completion	8 weeks and 16 weeks follow up CD and paper booklet with instructions on PR Practice 2*day for 15 min and apply at the onset of HFNS	Shallow breathing (SB): Digital videodisc with paper booklet Practice 2*day for 15 min and apply at the onset of HFNS Usual care (UC) group	Diary (HFNS frequency, severity, bother)	<i>ns</i> Adherence: 92%	PR vs. UC Frequency <i>d</i> =0.2 Severity: <i>d</i> =0.3 Bother: <i>d</i> =0.4 PR vs.SB Frequency <i>d</i> =0.1 Severity: <i>d</i> =0.2 Bother: <i>d</i> =0.1	0.9

CBT									
Mann et al, 2012 ¹³	UK	96 women after the end of cancer treatment with ≥ 10 HFs/wk for ≥ 2 months	6 weeks and 26 week follow-up Group CBT	Usual care	HFRS (HFNS frequency, problem rating) SSC monitoring (HFNS frequency)	Problem rating: CBT < TAU at post-t and FU	HFRS problem rating: d=0.6 frequency: d=0.2	0.9	
Duijts et al, 2012 ¹⁴	Netherlands	422 early stage cancer survivors	6 weeks and 6 month follow-up Group CBT	PE CBT/PE Usual care	HFRS (frequency, problem rating)	Problem rating: CBT, CBT/PE<TAU at post-t and FU Frequency: <i>ns</i>	Problem rating: CBT vs. TAU: d= 0.4, CBT/PE vs. TAU: d= 0.5	0.9	

Key: PSQI = WSCL=Wiklund Symptom Check List; Pittsburgh Sleep Quality Index; HFRDIS =Hot Flash Related Daily Interference Scale; MENQOL=Menopause-Specific Quality of Life; ISI=Insomnia Severity Index; Menopausal Symptom Questionnaire; MBSR=mindfulness-based stress reduction; SCL-90-R=Hopkins Symptom Checklist; PSS=Perceived Stress Scale; WHIIRS=Women’s Health Initiative Insomnia Rating Scale; KI=Kupperman Index; GCS=Greene’s Climacteric Scale; GHQ=General Health Questionnaire; STAI= Spielberger State/Trait Anxiety Index; MenQOL=Menopause Specific Quality of Life Questionnaire; SF-12= Short Form 12-Item Survey; BDI=Beck Depression Inventory-Primary Care; NCICTC=National Cancer Institute Common Toxicity Criteria